Aus der Abteilung für Experimentelle Anaesthesiologie
der Universität Düsseldorf
(Leiter: Prof. Dr. med. J.O. Arndt)

FENTANYLS ANALGESIC, RESPIRATORY AND CARDIOVASULAR ACTION IN RELATION TO DOSE AND PLASMA CONCENTRATION IN UNANAESTHETIZED DOGS.

DISSERTATION
Zur Erlangung des Grades eines Doktors der Medizin,
der Medizinischen Fakultät der Universität Düsseldorf

vorgelegt von
Dr.sc.agr. Ch. Parasher

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Introduction

Opiate receptors do not only mediate the action of opiates[1,2] but they constitute together with their natural ligands[3,4], the endorphins, a neuromodulator system in its own right[5-6]. This neuromodulator system is known to be linked with pain perception as well as with other brain functions like the control of vigilance[7], respiration[8] and circulation[9,10].

Given this background it does not appear tenable to differentiate between the desired analgesic properties of opiates and their untoward respiratory and cardiovascular side-effects unless the various components of opiate action can be shown to have different dose or concentration/effect relationships. Conclusive evidence in this direction, however, is lacking because of the difficulties in satisfying two basic requirements: one, the effects should be studied over the entire operating range of the receptor system i.e. up to saturation, which has not yet been attempted in man, and two, there should be no interaction with other drugs, a problem inherent in experiments on anesthetized animals[11,12].

With these stipulations in mind, the present experiments were designed to identify the doses and ranges of plasma concentrations at which fentanyl exerts its cardiovascular, respiratory and analgesic actions during spontaneous respiration in trained unanesthetized dogs. Fentanyl was chosen for its present popularity in clinical anaesthesia and because of the controversy relating to dose[13]. It will be shown that fentanyl's analgesic, cardiovascular and respiratory action develop in the same range of plasma concentrations.

Methods and materials

Thirteen mongrel dogs with an average body weight of 22(± 5)kg were studied. The dogs which were unrestrained and awake, were trained to lie quietly, in horizontal lateral position for all measurements.

The common carotid arteries were exteriorized in skin loops to facilitate blood sampling and the recording of arterial blood pressure. Four animals had electromagnetic flow probes chronically implanted around the ascending aorta for the continuous recording of stroke volume.

Surgery (exteriorization of the carotid arteries and thoracotomy for the implantation of the flow probes) was performed under chloralose anaesthesia (80 mg/kg body weight) and controlled ventilation at least five weeks before the first study. The cables from the flow probe were lead out through a skin tunnel between the scapulae.

The animals received analgesics and antibiotics following their surgery.

Measurements

Circulatory effects

Arterial blood pressure was recorded continuously with a Statham 537 transducer via a plastic cannula inserted into the carotid loop and heart rate with an ECG-triggered cardiotachometer.

In six experiments on four dogs, stroke volume was derived continuously by electromagnetic flow meter (Statham SP 2200). The flow meter was calibrated with saline before implantation.

Respiratory effects

Respiratory rate (by a mercury-in-silastic-gauge[14] around the thorax) and oxygen consumption ($\dot{V}O_2$) were measured continuously. The latter was achieved by passing air at 20 l/min by means of a precision pump through a transparent plastic hood placed over the animals' head. The oxygen consumption can then be calculated automatically from the air flow and from the O_2 difference (paramagnetic principle) between the in- and outflowing air[15].

Arterial blood gases and the pH were determined intermittently at specified time intervals.

Test for pain responses

Tail clamping with a hemostat was used as a pain stimulus. The test was evaluated in terms of the provoked increase in heart rate and arterial pressure.

Determination of fentanyl in plasma

Plasma was separated from whole blood by centrifugation and extracted with a mixture of hexane and ethanol (volume ratio 19:1), the former being purified by passing it twice through a glass column filled with 28/200 mesh silica gel. Extraction proceeded according to the method of Gillespie et al., 1981[16].

To account for losses during extraction, an internal standard was prepared by dissolving approximately 0.5 mg freeze dried fentanyl in 10 ml ethanol.

The average recovery of fentanyl was 94 $\pm$ 4.5 (SD) for duplicate estimations.

A Perkin-Elmer gaschromatograph F 22 equipped with a nitrogen detector was used. Separation was achieved with a column

(2m long and 2 mm in diameter) packed with 2 % OV-17 on a gas chrom Q80/100 mesh. The injector port and detector were maintained at 280°C, the column at 270°C. Flow rates for the carrier gas N_2, O_2 and H_2, were 80, 60 and 8.6 ml/min, respectively.

Experimental protocol

After setting up the recording system, the awake animals remained undisturbed in the lateral horizontal position with their heads under the plastic hood for a control period of at least one hour during which time all parameters were recorded continuously. This period enabled the animals to calm down as indicated by the low heart rate, blood pressure, and O_2 consumption levels (see fig. 1).

Fentanyl was then injected in doses of 2.5, 5, 20, 40 and 100 µg/kg every 5 min. Blood samples for the determination of gas tensions and fentanyl plasma concentrations were taken just before each succeeding dose and after the largest dose as indicated in Fig. 2. Each dose of fentanyl was injected within 30 - 45 sec.

Data analysis

To demonstrate the fentanyl effects and plasma concentrations in relation to the pre- and postinjection control periods, the averages ($\pm$ SE) were considered in relation to time and the effects determined in relation to the preinjection controls. The concentration/effect relationships were derived by plotting the changes from the preinjection controls against the corresponding concentration.

The Student T test for paired samples was employed for statistical analysis, differences between $p < 0.05$ being considered significant.

Results:

Fentanyl affected the respiration, circulation and the pain responses in the same dose range. As is seen in fig. 1 the effects increase after each fentanyl injection reaching a maximum or minimum after the fourth injection (40 µg/kg). The last dose (100 µg/kg) had no additional effect. Note that each data point reflects the effects of the preceeding injection.

There was a complete absence of the pain responses after the fourth injection but they gradually recurred during the post-injection period in parallel with the normalization of the other parameters, most of which reached their preinjection values between one and two hours after the last injection of fentanyl.

The pronounced drop in heart rate from approximately 75 beats/min during the control to 40 beats/min lead to a proportional reduction of cardiac output which in six additional experiments on 4 dogs, fell from 1760 ml (SE ± 160) by 800 ml or 45 % after the highest fentanyl concentration (see fig. 4). Curiously, in spite of this and the marked fall in arterial pO_2, the O_2-consumption declined only from 5.5 to 4.8 ml/kg/min in the face of spontaneous respiration.

As seen in fig. 3 these effects develop over a wide range of plasma fentanyl concentration between 2.5 and 500 ng/ml. The concentrations, determined five min after drug injection, correlate linearily with the dose. After the last dose the concentration falls initially quickly to approximately a tenth of its peak but later much slower from around 25 to 10 ng/ml between 30 and 120 min. It should be noted that the

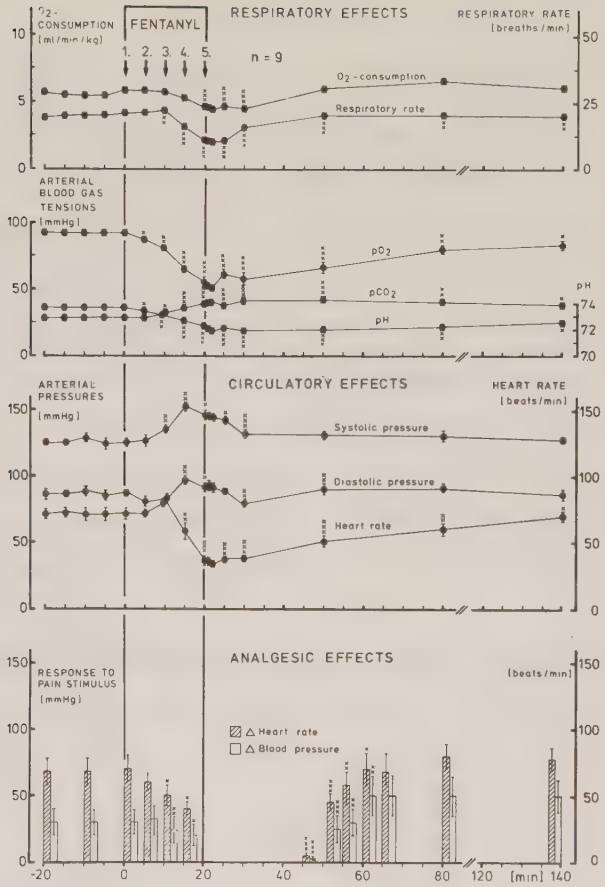

Fig. 1

Respiratory, cardiovascular and analgesic effects of fentanyl in unanesthetized, spontaneously breathing dogs. Averages (± SE) from 9 dogs which were awake during controls. Cumulative doses of fentanyl (2.5; 5; 20; 40 and 100 µg/kg) were injected at five minute intervals as indicated by the numerials. The data points at the time of injection reflect the effects of the previous dose. The increase in heart rate and blood pressure to tail clamping with a haemostat was defined as a pain response. T-test for differences to the preinjection controls, X=2P $<$ 0.05, XX $<$ 0.01, XXX $<$ 0.001.
All effects become obvious after the third injection and they reached their maxima or minima after the fourth dose since the last injection had no further effect. The parameters returned to their preinjection values between 60 - 90 minutes after the last injection.
The respiratory, cardiovascular and analgesic effects of fentanyl occured in the same dose range.

normalization of most of the parameters during the postinjection period in fig. 1 coincides with the slow decay of the plasma concentration, i.e. the effects of fentanyl decay when its plasma concentrations fall below 20 ng/ml and eventually fade when below 10 ng/ml.

One arrives at similar concentration range by looking at the concentration/effect relationship for the cumulative dose in fig. 3. Here the parameter changes from the control values in the awake state were related to plasma concentration. The first significant effects occur at plasma concentration in the neighbourhood of 5 ng/ml and all curves have minima or maxima at concentrations in the neighbourhood of 30 ng/ml. This is also true for the changes in cardiac output seen in the additional experiments in four dogs in fig. 4.

In unanesthetized dogs, the respiratory, cardiovascular and analgesic effects of fentanyl develop in the same concentration range and the maximum effects are attained at plasma concentrations at and around 30 ng/ml, i.e. all effects saturate so that higher concentrations do not have further effects.

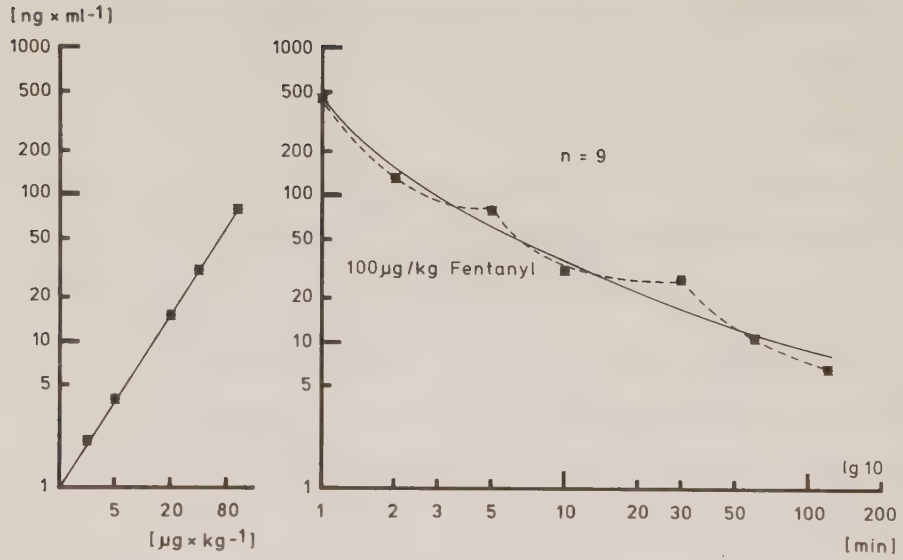

Fig. 2

Fentanyl plasma concentrations in unanesthetized, spontaneously breathing dogs.
Averages (± SE) of 9 experiments on 9 unanesthetized dogs. Fentanyl was injected intravenously in cumulative doses (2.5; 5; 20; 40 and 100 µg/kg body weight) at five minute intervals. Blood samples were taken five minutes after each injection and after the last injection as indicated on the graph. Note the double logarithmic scale. There is a linear relationship between dose and plasma concentration on the left and on the right a multi-exponential decay of the concentration with time.

Discussion

In unanesthetized, spontaneously breathing dogs fentanyl exerts its analgesic, respiratory and cardiovascular effects in the same range of plasma concentrations between approximately 5 to 30 ng/ml (2 to 6 x 10^{-8} molar). Plasma concentrations as high as 500 ng/ml have no further effects.

Was there an equilibrium between the plasma and brain concentrations in these experiments? For the measurements made five minutes after injection this is in all likelihood the case for the following reasons: The highly lipophilic fentanyl acts quickly because it rapidly penetrates the blood brain barrier. In rabbits, the brain concentration reach a maximum of 30 ng/g wet weight within 30 s and the ventricular liquor and plasma concentrations equilibrate within 5 min after injection of 20 µg/kg fentanyl and both decay in parallel thereafter[17]. In anesthetized (enflurane) dogs, the maximum cisternal liquor concentrations occured between 2 and 10 min after the injection of 10 and 100 µg/kg fentanyl and declined at the same rate as in plasma[11]. Finally the concentration equilibrium between plasma and brain is indicated also by the correspondence in the plasma concentrations at which the effects occured with the cumulative dose (five minute values) and at which they vanished in the postinjection period in the present experiments. The plasma concentrations therefore mirror by and large the actual brain concentrations.

For a concentration ratio of one tenth between plasma and brain tissue[18], the effective brain concentration can be estimated to range between 50 to 300 ng/wet weight of bet-

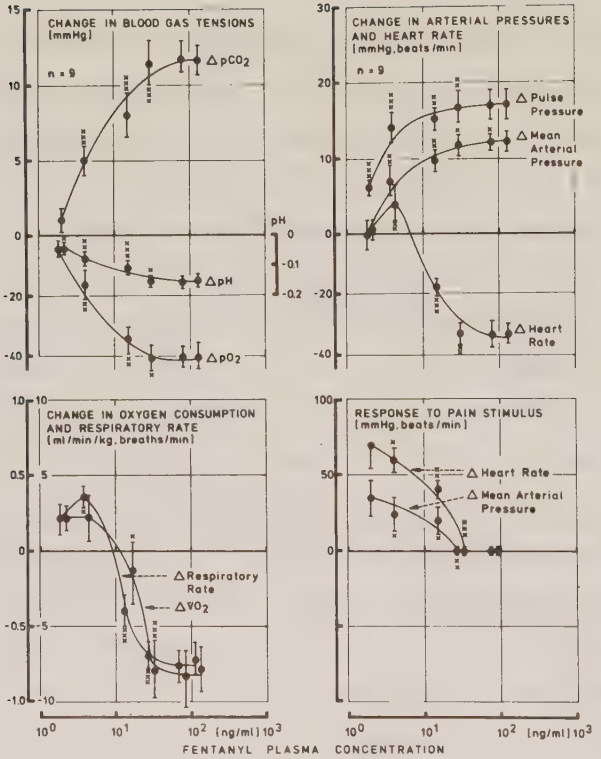

Fig. 3

Plasma fentanyl concentration/effect relationships of the respiratory, cardiovascular and analgesic action in unanesthetized, spontaneously breathing dogs.
Averages (± SE) from 9 dogs. Shown are the changes from the preinjection values in the awake state with the curves drawn by eye. Fentanyl (2.5; 5; 20; 40 and 100 µg/kg) was injected intravenously every five minutes. The increase in heart rate and blood pressure to tail clamping with a haemostat was taken as a pain response. X=2P $<$0.05, XX $<$0.01 and XXX $<$0.001 for differences of effects between one concentration to the next.
All curves are in the same concentration range with maxima and minima at fentanyl plasma concentrations at about 30 ng/ml.

ween 1.5×10^{-7} and 9×10^{-7} molar. Although direct evidence from fentanyl binding studies is lacking for the dog, the above estimates of brain concentrations very likely mark also the working range of the opiate receptors, i.e. of the receptor-mediated specific action of fentanyl. Quantitatively similar results as described here could be obtained by the selective perfusion of fentanyl through the fourth cerebral ventricle in unanesthetized dogs where the effects (bradycardia, EEG synchronisation with sleep-like states) saturated and could stereospecifically be reversed by the laevoisomer of naloxone but not by its pharmacologically inactive dextroisomer, observations, strongly suggesting opiate receptors as mediators[7,12]. Since in those experiments fentanyl plasma concentrations of 4.4 ng/ml were ineffective, it can safely be presumed that the threshold concentration of which specific fentanyl effects occur is in agreement with the present observations as being in the vicinity of 5 ng/ml plasma or at a brain concentration of around 50 ng/g wet weight. At the upper end of the spectrum, the opiate receptors saturate at plasma concentrations of 30 ng/ml or at brain concentrations of 300 ng/g wet weight.

Saturation of the binding sites implies that, in dogs, it is neither feasible to separate the desired analgesic from any untoward depressant effects on respiration and circulation in the pharmacological dose range of fentanyl nor is it possible to attain a different quality of action with doses necessary for the complete occupation of the binding sites.

The attainment of a certain endpoint of the action of fentanyl,

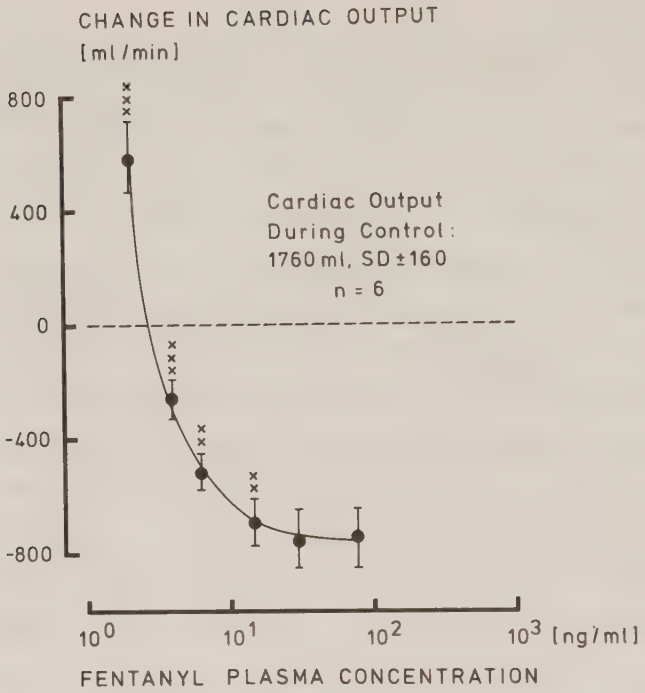

Fig. 4

Plasma fentanyl concentration/effect relationship on cardiac output in unanesthetized, spontaneously breathing dogs.
Averages (± SE) from 6 experiments on 4 dogs with chronically implanted electromagnetic flow probes (ascending aorta). Cumulative doses of fentanyl (2.5; 5; 20; 40 and 100 µg/kg) were injected intraveneously at five minute intervals. Change in cardiac output from the preinjection values in the awake state. X=$2P < 0.05$, XX < 0.01 and XXX < 0.001 for differences of effects between one concentration to the next.
There is a concentration-related fall in cardiac output with a minimum plasma fentanyl concentration of about 20 ng/ml.

that is compatible with adequate physiological function, has been previously demonstrated in particular for cardiovascular effects[7,19]. This has not been the case in respect to respiratory function, because controlled ventilation was usually instituted when signs of respiratory depression occured. It was therefore surprising that all animals resumed spontaneous respiration with an adequate O_2-supply after an untreated temporary respiratory arrest lasting usually 1 min. At saturation, respiratory rate, arterial O_2-tension, heart rate and cardiac output were nearly halved when compared with the preinjection controls in the awake state, but in spite of this, oxygen consumption fell only slightly from 5.5 to 4.8 ml/kg/min.

It is also worth mentioning that the low oxygen consumption during the administration of fentanyl did not fall short of the basal metabolic rate values. In these dogs studied in the quiet, awake state on 201 separate occasions over a period of several months, an average oxygen consumption of 3.98 ml/kg/min ($\pm$ SE 1.01) was measured. These values are in agreement with previous measurements in trained dogs[20], and correspond also with calculations based on the metabolic rate formula ($\dot{V}O_2$ = 10.15 x weight in $kg^{0.73}$)[21]. Fentanyl even in doses far higher than those necessary to achieve complete analgesia, obviously does not jeopardize an adequate oxygen supply in dogs.

It should be stressed, however, that this may hold only under the special experimental conditions of this study in which the interaction between fentanyl, sedatives or anesthetics was excluded. In anesthetized dogs (enflurane), the

actual pCO_2 increased maximally 25 mm Hg which is much more than the 7 mm Hg increase in the present experiments after the injection of 10 µg/kg fentanyl even though the threshold plasma concentration at approximately 1 ng/ml was almost identical in both studies[11].

Fentanyl possibly potentiates the inhibitory action of general anesthetics on homeostatic control mechanisms via a central interaction with anesthetics. For example, baroreflex function is normal and the blood pressure stable, in spite of the profound bradycardia which developed in the dogs during the full action of fentanyl, whereas these reflexes are almost abolished and severe hypotension ensues when fentanyl acts together with halothane[12].

Fentanyl alone does not curtail the metabolic and homeostatic control of the cardio-respiratory system below physiological limits. The slowing of the heart and respiration with the accompanying increase in pCO_2 resemble the automatic manifestations of slow wave sleep[20] and may thus be a consequence of fentanyl's hypnotic action[7]. Curiously, the influences of central activity on breathing are often overlooked while those of carbon dioxide, which is but one of several respiratory control loops, is given undue emphasis in the interpretation of anesthetic effects[20]. The absence of a threshold for CO_2 ("apnoea point") in many awake men, its invariable presence during anesthesia, and the insentivity of the threshold level to the concentration of anesthetics is a case in point[21]. By the same token, it is presumably the combined action of fentanyl with sedatives and/or anesthetics that

jeopardize adequate breathing.

Are these observations applicable also to man? It would appear that comparable data to those presented here are not available for man. But for complete analgesia, man apparently requires similar plasma fentanyl concentration as dogs. Patients undergoing open-heart surgery, who have been anesthetized with fentanyl alone (70 µg/kg injected in five minutes) and ventilated with pure oxygen, had on the average, peak plasma concentrations of 100 ng/ml and two hours later, while still analgesic, 25 ng/ml[13]. Even though the complete dose or concentration/effect relationship remains obscure in man, it is nevertheless presumed that these plasma fentanyl concentrations are, on the average, sufficiently high to saturate opiate bindung sites and thus obtain a maximum effect.

How to achieve the maximum effect from fentanyl, a drug having a high lipid affinity and therefore prone to rapid redistribution[17,21], is a matter of debate. Even with the so-called high doses presently advocated for "stress-free anesthesia"[13], the plasma concentration (at least in dogs and in all likelihood man), is still within the operation range of the opiate receptor system. These doses are therefore unlikely to have a different quality of action such as anesthetic properties in the strict sense, because the concomittant plasma concentration are far below the ranges at which opiates have nonspecific side-effects seen for example, on the myocardium in the 10^{-4} to the 10^{-3} molar range[23]. The doses which are currently quoted as being high are, for pharmacokinetic reasons, only high in relation to the duration, but not the quality of action.

At least in unanesthetized dogs we could show that fentanyl exerts its analgesic, respiratory and cardiovascular action in the identical range of plasma concentrations, in which case it seems impossible to separate the desired analgesic effects from the untoward cardiovascular and respiratory side-effects.

Summary:

In dogs plasma concentration/effect relationships for fentany were determined in order to see if the operating ranges for the analgesic, respiratory and cardiovascular component of action are the same or not.

To avoid drug interactions we used trained unanesthetized spontaneously breathing dogs. After a control period in the awake state, fentanyl (2.5 to 100 µg/kg) was injected cumulatively and its effects studied on pain responses (heart and blood pressure changes to tail clamping), respiration (respiratory rate, oxygen consumption, blood gase tensions), and circulation (heart rate and blood pressure).

Plasma concentration/effect curves were derived by relating the parameter changes from the awake state to the corresponding plasma concentration which ranged between 2.5 to 500 ng/ml. Most effects followed the same curves and reached a maximum at plasma concentrations at and around 30 ng/ml. Oxygen consumption fell only slightly by 0.7 ml/kg per min and remained well above the basal metabolic rate even though cardiac output, heart rate, respiratory rate and arterial oxygen tension were almost halved during the full action of fentanyl.

In dogs, fentanyl's analgesic action cannot be separated from its respiratory and cardiovascular effects. All effects are maximal at a certain plasma concentration, a phenomenon, suggesting saturation of the opiate receptors.

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Curriculum Vitae

Was born as son of Late Pt. Puran Mal Parasher and his wife Smt. Nihali Devi ,on 1 March,1942.

In the year 1949-54 and 1954-60 visited the "Govt. Primary" and "Govt. H/S Kharkhoda respectively and from 1960-62 Pre-University examination.

Visited Banares Hindu University from 1962-67 and acquired B.Sc. and M.Sc.agr. degrees.After that from 1967-70 visited the University of British Columbia in Vancouver,Canada and was conferred the degree of Master of Science "M.S.".

From 1970-73 joined the University of Stuttgart-Hohenheim and received my Ph.D. After that from 1973-76 worked on secondary effects of environmental chemicals in Biologischen Bundesanstalt Berlin and from 1976-77 in the Dept. of Toxicology,Universität Düsseldorf on heavy metal toxicology.

Resumption of medical studies at Trinity College Dublin and completion of the same from Punjab University in 1980 along with internship and house job til July,1981.

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